Migraine: A disorder of metabolism?

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Abstract

The treatment and prevention of migraine within the last decade has become largely pharmacological. While there is little doubt that the advent of drugs (e.g. triptans) has helped many migraine sufferers to lead a normal life, there is still little knowledge with respect to the factors responsible for precipitating a migraine attack. Evidence from biochemical and behavioural studies from a number of disciplines is integrated to put forward the proposal that migraine is part of a cascade of events, which together act to protect the organism when confronted by a metabolic challenge.

Keywords: Migraine; Insulin; Glucose; Insulin resistance; Nutrition; Hypoglycemia

Introduction

Migraine is a chronic neurovascular disorder that is characterized by recurring headache of unilateral onset, photophobia, phonophobia and autonomic disturbances [89], (IHS, 2013). A systematic review of population-based studies reporting migraine prevalence found that the incidence of chronic migraine was estimated to range from 0 to 5.1% [152]. However, sex differences have been noted with women up to four times more likely to be affected than men [133].

Historically, migraine was thought to be a vascular disorder. The association between migraine and vascular diseases such as hypertension and ischemic brain injury and vascular disorders such as coronary heart disease and stroke is well known [222]. However, the advent of new technology has confirmed that migraine pathophysiology is associated with disturbances in many parts of the brain including the hypothalamus, thalamus and brainstem [80].

The recommended treatment and prevention strategies for migraine within the last decade have become largely pharmacological. The discovery of selective 5-hydroxytryptophan agonists has provided many migraine sufferers relief from the severely debilitating symptoms, which often result in the individual being unable to carry out even the most basic of functions during an attack [79,80]. Prophylactic treatment using a range of drugs (e.g. β-blockers, flunarizine, valproic acid and topiramate), is also not uncommon. However, while drugs are often prescribed for the prevention or management of migraine, pharmacotherapy is often unsuccessful in preventing a recurrence of symptoms in migraine sufferers [63].

The study of migraine is made difficult by the lack of an animal model that translates fully the clinical symptoms of migraine [188], the episodic nature of the attacks [1], and the observation that the migraine 'trigger' can be of nutritional, psychological, hormonal or behavioural origin [47,57,105,176,235,112,113]. To date, researchers have been unable to identify a set of triggers common to all migraineurs. Indeed, every case of migraine appears to have its own set of unique triggers making treatment and prevention of the condition difficult. A summary of some of the most common migraine triggers is provided in Table 1.

Table 1 Summary of the reported psychological, nutritional, hormonal, behavioural and environmental migraine triggers [145,134,114,112,113,70].

Group	*Migraine trigger*
Psychological	Emotional stress
Hormonal	Menstrual cycle, oral contraceptives
Behavioural	Exercise, disrupted sleep, fasting, skipping meals, dehydration
Environmental	Bright lights, odour, weather changes, cigarette smoke, gasoline

Nutritional	Cheese, milk, citrus, monosodium glutamate, aspartame, glucosamine, chocolate, ice-cream, alcohol, white wine, red wine, banana, coffee, nitrates (e.g. sausage, bacon)

A significant association between polymorphisms in the insulin receptor gene and migraine pathogenesis has been confirmed [143]. Moreover, there is increasing evidence that altered energy metabolism and utilization may hold the key to understanding the pathogenesis of migraine (e.g. [105,176]. However, if this is true then it should be possible to establish a link between the known migraine triggers and some alteration in energy metabolism and utilization.

The aim here is to examine the effect (if any) of the most commonly reported migraine triggers on glucoregulation. The review will consist of three sections. The first section will provide a minor review of the biochemical processes usually activated during feeding and fasting in non-migraineurs. This information has been included in order to assist those unfamiliar with the feeding and fasting literature. Then an overview of the most salient pathways of metabolism known to contribute to migraine will be presented. Lastly, data from human and animal studies will be used in order to argue that the common factor linking the known migraine triggers may be an underlying ability, albeit variable, to promote the development of a metabolic challenge.

Section 1: Metabolic effect of feeding and fasting

The human body needs to be able to function when food is not available. Thus, the metabolism of glucose, the main energy source for cells, is a highly regulated mechanism. When food is available, glucose is converted by glycolysis into pyruvate and lactate in the cytosol and any excess glucose is converted to glycogen by glycogenesis and stored. Alternatively, when food intake is low the stored glycogen is converted back to glucose by glycogenolysis [22].

Insulin, a peptide hormone released by beta cells in the pancreas, has a key role in the utilization of glucose, amino acid and free fatty acids [53]. In order for glucose to gain entry to most cells it must be transported by an active mechanism, which is controlled by insulin receptors in the cell membrane. However, cells located in the brain are an exception to the rule and many types of cells do not need insulin to absorb glucose [22].

After a meal high in carbohydrate the levels of glucose and insulin are significantly elevated and the level of plasma insulin remains elevated until the plasma glucose level begins to drop, which can take several hours [22]. In contrast, during fasting insulin secretion is markedly reduced and cortisol, a glucocorticoid under the control of the hypothalamic-pituitaryadrenal (HPA) axis is elevated in order to reduce glucose utilization and transport and promote gluconeogenesis [53].

Fasting and extended periods when food is not available can result in the body's energy needs being met by gluconeogenesis, which produces glucose-6-phosphate from lactate, amino acids, free fatty acids (FFA) and glycerol from stores located in adipose tissue [22]. All cells with the exception of brain cells can metabolize FFA. If the period of fasting is prolonged the liver, in order to maintain the brain's glucose requirements, has the ability to convert FFA to ketone bodies. The brain can adapt to the usage of ketone bodies as fuel and during periods of extreme starvation can obtain up to 75% of its glucose requirements from this energy source [22].

Glucose transport

The brain is highly dependent on glucose from the circulation to meet its energy needs. Glucose transport from the circulation across the capillary endothelial surface occurs via the GLUT1 transport protein and the subsequent transport of glucose from the interstitium to either neuron or glial cells occurs via the GLUT3 transporter [31].

The glucose transporter number on the capillary endothelial surface is regulated largely by the plasma glucose concentration. Under normal conditions approximately twice the amount of glucose required to meet the brain's metabolic needs is transported. However, due to the brain's limited capacity for storage of glucose as glycogen, any unused glucose is transported back into the circulation [31].

GLUT2 acts as a transmembrane carrier protein that facilitates glucose movement across cell membranes. Moreover, GLUT 2 also acts as a carrier for fructose and glucosamine and is primarily found in cell membranes in the liver, kidney, small intestine and pancreas. Feeding and an increase in glucose concentration promote upregulation of GLUT2 mainly at the brush border membrane. In the pancreas, GLUT2 significantly influences insulin secretion by regulating the entry of glucose into pancreatic cells [122].

GLUT2 activity has been noted in the hypothalamic areas of the brain. Data from animal studies suggests that GLUT2 acts as a glucose sensor in the (ARC and PVN not defined yet. Need to replace ARC and PVN with: hypothalamic arcuate nuclei (ARC) and paraventricular nuclei (PVN).)ARC and PVN. GLUT2 receptor activation plays a significant role in the hormonal control of food intake in the hypothalamus by detecting and signaling glucose to adapt to meal size. Moreover, the evidence suggests that the amount of food consumed is significantly altered in the absence of any change in feeding frequency [212].

In contrast, GLUT4 is the major insulin responsive transporter (see Fig. 1). GLUT4 expression is primarily observed in muscle and fat cells and the principle role of GLUT4 is to promote whole-body glucose homeostasis [36]. A high expression of GLUT4 can occur when the level of blood glucose is low. However, the level of GLUT4 expression can also be a determinant of insulin-induced insulin sensitivity [15] with a reduction in GLUT4 content also indicating insulin resistance [37].

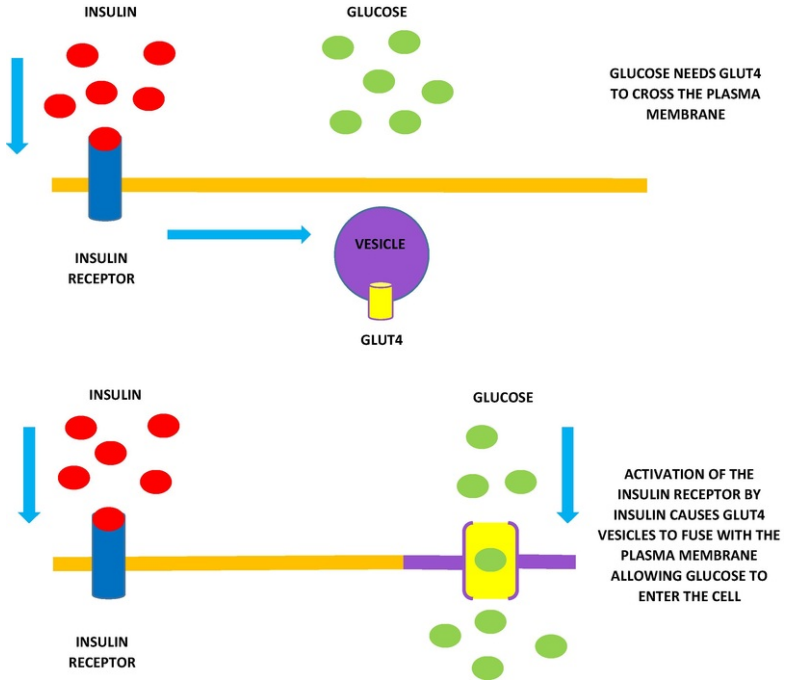

Fig. 1 Insulin-dependent GLUT4 glucose transport.

Insulin is a key regulator of glucose homeostasis and insulin resistance is a condition whereby a normal amount of insulin produces a sub-normal response. Cells become resistant to the actions of insulin and are unable to use it, which invariably leads to hyperglycemia. In order to circumvent the hyperglycemia pancreatic beta cells produce even more insulin, which over time promotes hyperinsulinemia [179].

The insulin-sensitive GLUT4 isoform was initially thought to be localized to vascular structures within the (VMH not defined. VMH needs to be replaced with: ventromedial hypothalamus (VMH))VMH, which could suggest a role for insulin in this specific brain area [156]. However, later work confirmed that GLUT4 and GLUT8 are expressed in several areas including cortex, amygdala, hippocampus, cerebellum and hypothalamus prompting the authors at the time to conclude that cerebral insulin may increase the uptake of glucose in these specific brain areas [9].

Hypoglycemia

When the level of glucose transport is insufficient to meet the brain's metabolic needs hypoglycemia can develop [32,31]. The normal physiologic counter regulatory response to hypoglycemia includes secretion of glucagons and pancreatic polypeptide from the pancreas; cortisol from the adrenal cortex; norepinephrine from sympathetic post-ganglionic nerve terminals; epinephrine from the adrenal medullae; adrenocorticotrophic hormone (ACTH) by the hypothalamus and growth hormone by anterior pituitary gland. Moreover, the stimulatory effect of hypoglycemia involves (among other things) an elevation in histamine and the modulation of corticotrophic releasing factor and/or vasopressin [78,232]. The acute metabolic effect of the combined neuroendocrine response involves increased hepatic glycogenolysis/gluconeogenesis together with elevated rates of lipolysis and decreased glucose utilization outside of the brain [58].

Symptoms of hypoglycemia are partly sympathetic (e.g. sweating, tremor, palpitations, sensations of hunger, restlessness and anxiety) and thought to be linked to the release of catecholamines. Other symptoms caused by an insufficient supply of glucose to the brain resulting in neuroglucopenia include blurred vision, weakness, slurred speech, vertigo and difficulties in concentration [25]. There are relatively marked differences in regional glucose concentrations during hypoglycemia with higher glucose levels being observed in the thalamus, hypothalamus and brainstem. [168].

Hormonal control of feeding

Feeding behaviour is largely dependent on the efficient performance of cortisol and insulin and any dysregulation in either of these two hormones has the potential to alter a large number of biochemical events. Early work suggests that a low-moderate level of cortisol is required to stimulate appetite [42], and insulin release [181], while a concomitant rise in insulin stops feeding [236].

The effects of insulin may be mediated, in part, through the regulation of hypothalamic neuropeptide Y (NPY) synthesis and release [213]. Fasting promotes an elevation in glucocorticoids [87], which increases the transcription rate of NPY mRNA [55,234]. The release of NPY in turn raises the plasma insulin level [120,146,233] in the (Replace the words: ventromedial hypothalamus (VMH) with: VMH)ventromedial hypothalamus (VMH) [234]. Alternatively, insulin acts locally in the (Replace the words: hypothalamic arcuate nucleus (ARC) with: ARC)hypothalamic arcuate nucleus (ARC) to inhibit NPY gene expression [198].

An important effect of NPY, a 36-amino sequence pancreatic polypeptide, on the (Replace the words: hypothalamic paraventricular nucleus (PVN) with: PVN)hypothalamic paraventricular nucleus (PVN) is its ability to induce feeding [150] and drinking behaviour [208,209]. NPY-induced feeding behaviour in the PVN appears to specifically increase carbohydrate intake [208], and a lack of glucocorticoids by inhibiting NPY release in the PVN notably decreases carbohydrate intake [219].

The ARC contains glucose-sensitive NPY-containing neurons. The purpose of these neurons is to detect an elevation or reduction in the glucose concentration in the brain and subsequently reduce or stimulate NPY-induced feeding, respectively [150]. Thus, glucose utilization may constitute an important signal, either direct or indirect, in the modulation of NPY production in the hypothalamus [2].

Animal data has revealed that NPY may be involved in mediating the effects of serotonin or 5-hydroxytryptamine (5-HT), suggesting some functional interaction between the serotonergic and NPYergic systems [187]. 5-HT is biochemically derived from tryptophan (Trp) and local injection of NPY in the VMH can significantly reduce the concentration of 5-HT by acting through Y1 receptors to modulate the rate of synthesis of Trp hydroxylase, an enzyme necessary for the conversion of Trp to 5-HT [106].

In the CNS, 5-HT has a number of functions including regulation of mood and appetite. 5-HT is a powerful anorectic agent [61] with an increase and decrease in 5-HT known to inhibit and promote feeding, respectively [190,237]. The effect of hypothalamic 5-HT stimulation is specific to carbohydrate intake [127]. The release of 5-HT can preferentially inhibit the ingestion of carbohydrate more than food containing protein or fat (e.g. [129,128,126], in a selective and dose-dependent manner [127].

There is usually an antagonistic relationship between NPY and 5-HT. The level of 5-HT is usually reduced during fasting when the level of cortisol and NPY is elevated. Following ingestion of a high carbohydrate meal the level of 5-HT and insulin is elevated and the level of NPY reduced [53] (Reference for Dallman et al., 1995 provided and will need to be added to reference list.)(Dallman et al., 1995). A significantly raised insulin can affect the uptake of Trp and influence the synthesis of 5-HT in the brain [18]. Food intake can alter the level of transmitter that serotoninergic neurons release such that carbohydrates with a higher glycemic index may have a greater serotoninergic effect than carbohydrates with a low glycemic index(Please add reference 206 (i.e. Smolders et al. 2001) here so that it reads: (136, 206)) [136].

In rodents, 5-HT above 20 mg/kg can induce apparent hypoglycemia. The hypoglycemic effects of 5-HT are strongly antagonized by methysergide, a known 5HT1 agonist and 5HT2 antagonist, partially inhibited by ketanserin a selective 5-HT2 receptor antagonist known to promote insulin resistance, and unaffected by tropisetron (ICS 205-930) a 5-HT3 receptor antagonist. Thus, the hypoglycemia induced by 5-HT may be mediated by both the 5-HT1 and 5-HT2 receptors [240,205,76].

In non-diabetic mice, 5-HT can induce a dose-dependent hypoglycemia and significant elevation in serum insulin concentration. 5-HT can significantly inhibit glucose-induced hyperglycemia and increase glucose-stimulated insulin release. However, a similar effect was not noted in streptozotocin-induced diabetic mice with 5-HT found to have no effect on either the level of glucose or insulin. Thus, 5-HT-induced hypoglycemia is specifically linked to a significant increase in serum insulin concentration [215].

The serotonin 5-HT3 receptor, a ligand-gated ion channel, when activated can induce Ca2+ influx [189]. In pancreatic islet cells, an increase in systolic free calcium concentration is critical for secretagogue-induced insulin release [60]. Thus, activation of 5-HT3 receptors may promote insulin release by stimulating calcium (Ca2+) influx.

In non-diabetic mice peripherally administered 5-HT can induce a marked increase in the plasma glucagon level. However, the hyperglucagonemic effects of 5-HT is only associated with activation of 5-HT2 receptors [241]. It is known that glucagon leads to a decrease in hepatic glutathione (GSH) synthesis that in turn is associated with decreased postprandial insulin sensitivity [170]. Thus, the 5-HT2 receptor may increase the glucose level by altering insulin sensitivity during periods of severe hypoglycemia.

Section 2: Pathways of metabolism in migraine

Early work revealed that an elevation in FFA and ketone bodies often precedes a migraine attack [91]. Similarly, an elevation in FFA, glycerol concentrations, growth hormone, cortisol and ketone bodies can

also occur during a migraine attack [203]. Indeed, hypercortisolism is a common finding in migraine patients [242]. The elevation of plasma FFA was noted together with changes in blood glycerol concentrations and insulin was depressed, which when considered together is consistent with a metabolic stress response [91,203].

Glyceryl trinitrate

The administration of glyceryl trinitrate or nitroglycerin (GTN) has proven to be an effective method for triggering a migraine attack in humans. In the last few years the use of GTN in clinical trials has been refined [101,102,103,104] and the technique is now regarded to be a reliable method [1] for inducing a spontaneous migraine attack with a latency of several hours [103,204,218].

The release of 5-HT, a monoamine neurotransmitter that improves insulin sensitivity [94], is known to be impaired in migraine [34]. The level of 5-HT in the hypothalamus, mesencephalon, pons and medulla of rodents treated with GTN demonstrate a delayed (4 h) decrease in medullary and pontine levels of 5-HT [218]. Although, estrogen administration was shown to modulate the basal expression of transmitters and block the GTN effect [166].

Nitric oxide

GTN is a nitric oxide (NO) donor [103] that acts directly and/or indirectly on the central nervous system through the release of NO [218]. NO or parts of the NO activated cascade are known to play a key role in the development of headache and migraine [101].

The primary role of NO is to help control blood flow to nearly every part of the body. NO is a potent vasodilator that influences the functioning of many organs including lungs, liver, kidney, stomach and heart. NO is produced by many cells in the body. However, the production of NO by vascular endothelium is particularly important in the regulation of blood flow [110].

NO is synthesized from L-arginine (Arg) in a reaction catalyzed by NO synthase (NOS). Furthermore, histamine by promoting Ca2+ release can activate NOS [3,123]. An increase in NO and histamine is commonly observed in migraine. Additionally, the level of NO and histamine is often elevated during a migraine attack [158]. An overview of NO synthesis is provided in Fig. 2.

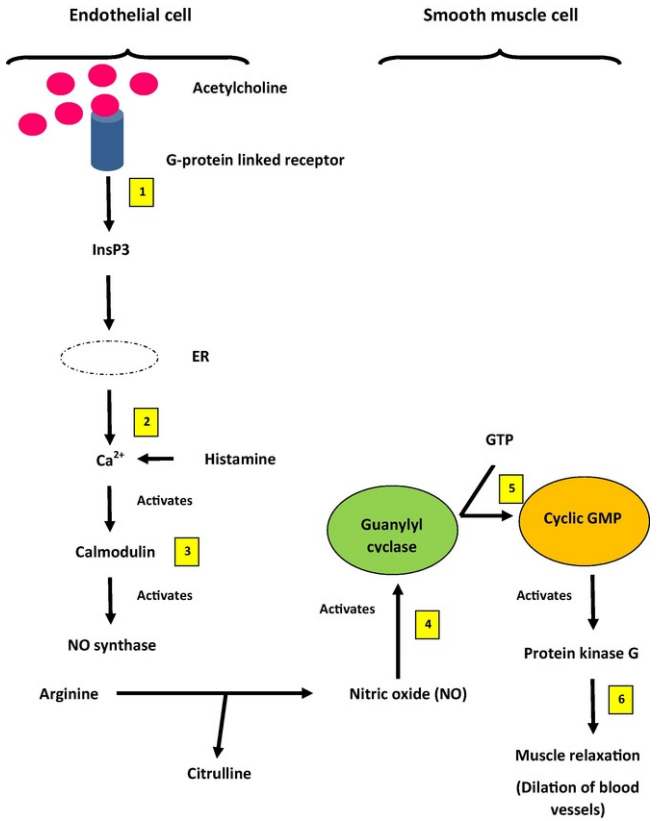

Fig. 2 Nitric oxide. (1) The binding of acetylcholine to G protein receptors causes inositol 1,4,5-trisphosphate (InsP3) production (2) and Ca^{2+} release from endoplasmic reticulum (ER). (3) The release of Ca^{2+} activates calmodulin which activates nitric oxide (NO) synthase and produces NO. (4) NO diffuses from endothelial cell into adjacent smooth muscle cells. (5) In smooth muscle cell, NO activates guanylyl cyclase to make cyclic GMP (cGMP). (6) cGMP activates protein kinase G, which phosphorylates several muscle proteins to induce muscle relaxation.

Rodent studies have shown that NO can inhibit glucose transport and metabolism with glucose uptake and lactate output noted to be 30% and 60% lower in GTN treated animals compared to controls [125]. Furthermore, the basal activity of NOS is significantly higher in diabetic compared to non-diabetic gastric glands [43].

Administration of N omega-nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor, promotes a marked and immediate increase in glucose-stimulated insulin release in the absence of any alteration in Ca2+ flux, both in vitro and in vivo. Furthermore, L-NAME administration can significantly inhibit the release of glucagon when applied in a glucose-free environment. Thus, one of the actions of NO may be to increase the level of glucagon by suppressing glucose-stimulated insulin release [4].

Histamine

At least four histamine receptors denoted by H1, H2, H3 and H4 have been identified [238]. Histaminergic neurons are involved in the mediation of the insulin/hypoglycemia-induced release of ACTH and beta-endorphin and this effect is mediated via activation of postsynaptic H1-receptors and, to a lesser extent, H2-receptors [109]. Activation of H1 [69,160] and inhibition of H3 [192] receptors in VMH and PVN may suppress food intake and increase the level of plasma glucose [157] by activating glycogenolysis during energy depletion [192].

One function of astrocytic histamine receptors in vivo may be the stimulation of glucose release from astrocytes, a process mediated by increased intracellular free Ca2+. Histamine's glycogenolytic effect is significantly reduced in the absence of extracellular Ca2+ and can be completely blocked by mepyramine, a H1 receptor antagonist [144]. Interestingly, the serotonin 5-HT3 receptor, a ligand-gated ion channel, when activated can induce Ca2+

influx [189].

A large number of H3 receptors have been observed in the cerebral cortex, amygdala, striatum, hippocampus, thalamus and hypothalamus [159]. The role of the H3 receptor may be to regulate the synthesis and release of histamine [221]. The H3 receptor can (among other things) inhibit the release of histamine [12] and 5-HT in cortex [194,67], which could potentially alter 5-HT receptor activity and insulin sensitivity.

Calcitonin gene-related peptide

GTN administration can promote the release of calcitonin gene-related peptide (CGRP), a 37 amino acid intrapancreatic neuropeptide released from the heart [97] and trigeminal sensory nerves [66]. The administration of CGRP can trigger a spontaneous migraine attack [124,13,211] and CGRP receptor blockade is an effective anti-migraine strategy [79]. However, pre-treatment with kynurenine (KYN) and (Replace the acronym KYNA with: kynurenic acid (KYNA))KYNA can attenuate the GTN-induced changes in CGRP immunoreactivity in the rat caudal trigeminal nucleus, which suggests that KYNA may alter trigeminal nociception [50,224].

CGRP acts on islet hormone secretion by significantly inhibiting and stimulating insulin concentration at low and high concentrations, respectively [90]. When CGRP is administered intravenously the level of basal glucose concentration is increased and the glucose rise after OGTT is enhanced. CGRP promotes a significant increase in the level of plasma glucose and subsequently plasma insulin concentration. Thus, an elevated CGRP may promote hyperglycemia, which in turn causes secondary hyperinsulinemia [147].

Rodent studies have confirmed that CGRP can inhibit insulin stimulated glucose transport [96] by reducing tissue glucose response to insulin [66]. CGRP is a potent inhibitor of muscle glycogen synthesis and may cause insulin-resistance upon activation of skeletal muscle sensory nerves [130].

Tryptophan-kynurenine pathway

Tryptophan (Trp), one of the 9 essential amino acids humans are incapable of synthesizing, is metabolized via two non-protein pathways: methoxyindole and KYN. Moreover, the availability of Trp as a substrate for both pathways is influenced by the level of FFA's, which release plasma Trp from their bond with albumin [162].

Trp is required for the synthesis of 5-HT [41], with the conversion from Trp to 5-HT ~~catalysed~~ catalyzed by the rate-limiting enzyme Trp hydroxylase [106]. However, only 5% of the available Trp is used to synthesize 5-HT via the methoxyindole pathway [54]. The major route of Trp metabolism being the formation of KYN, ~~catalysed~~ catalyzed by rate-limiting enzymes Trp 2,3-dioxygenase 2 (TDO2) or indoleamine 2,3-dioxygenase 1 (IDO1). At least 95% of the available Trp is metabolized via the Trp-KYN pathway [54], which generates several neuroactive and immunomodulatory metabolites (See Fig. 3).

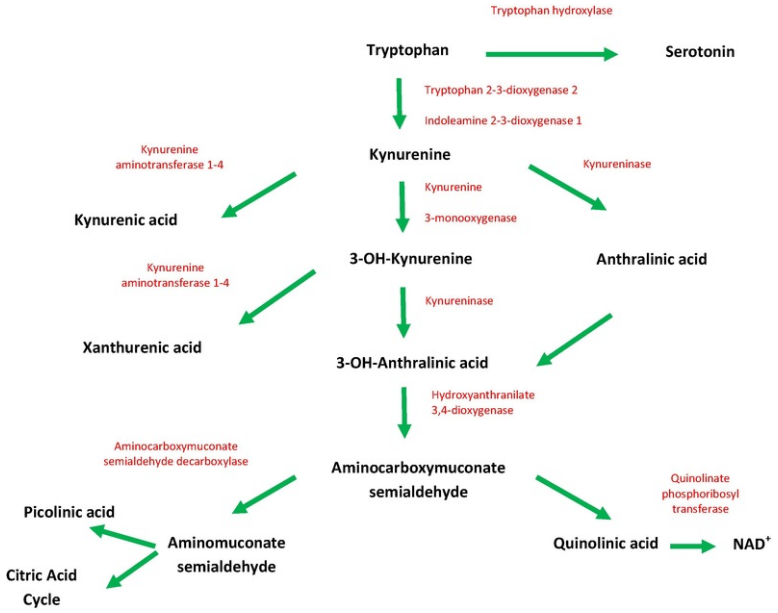

Fig. 3 The kynurenine pathway. Tryptophan is oxidized by cleavage of the indole-ring initiated either by tryptophan 2,3-dioxygenase 2 (TDO2) or indoleamine 2,3-dioxygenase 1 (IDO1). Kynurenine (KYN) is the first stable intermediate formed. There are several neuroactive intermediates generated before the final product, nicotinamide adenosine dinucleotide (NAD) is achieved. These comprise the free-radical generator, 3-OH-anthranilic acid (3-HANA), the excitotoxin and N-methyl-D-aspartic acid (NMDA) receptor agonist, quinolinic acid (QUINA), the NMDA receptor antagonist, kynurenic acid (KYNA), the neuroprotectant picolinic acid (PICA), and xanthurenic acid (XA), which has been linked to insulin resistance.

The conversion of Trp to KYN is regulated by enzymes influenced by pro-inflammatory factors and glucocorticoids. TDO2, which has been observed primarily in the liver and brain, is induced in the liver by Trp and glucocorticoids [135]. Thus, an increase in the release of cortisol, a glucocorticoid that becomes immediately elevated when the organism is under stress, could upregulate activity of Trp to KYN metabolism [162]. Alternatively, IDO1 has been found in several extrahepatic tissues including the brain. IDO1 can be up-regulated by cytokines and proinflammatory agents such as lipopolysaccharides, amyloid peptides, HIV proteins and tumor cells. However, interferon-gamma (IFN-γ) is the most potent stimulant of IDO1 and of interest here is the finding that IFN-γ can activate IDO1 mRNA accumulation in rat pancreatic islet cells [135].

Tryptophan-kynurenine pathway and receptor activity

Overactivation of NMDA glutamate (Glu) receptors has been observed in migraineurs [51,52]. Moreover, Glu has been implicated in migraine pathogenesis largely because it is known to play an important role in cortical spreading depression and activation of the trigeminal system (Csati et al., 2012), [65].

Activation of NMDA receptors promotes Ca2+ influx into cells, which subsequently promotes the formation of NO [131]. However, KYNA can inhibit the synthesis of NO. Similarly, 3-OH-anthranilic acid (3-HANA), at sub-millimolar concentrations can inhibit the expression and activity of inducible NOS (iNOS), which catalyzes the conversion of Arg to NO [41].

When NMDA and metabotropic Glu receptors are activated, arachidonic acid (AA), an unsaturated fatty acid, is released from phospholipids in an action catalyzed by the enzyme phospholipase A_2 [29]. Metabolites of the KYN pathway such as KYNA can inhibit while (Define acronyms QUINA and XA: quinolinic acid (QUINA) and xanthurenic acid (XA))QUINA and XA activate, NMDA Glu receptors [167]. Both QUINA and (Define acronym PICA: picolinic acid (PICA))PICA stimulate iNOS and together with 3-hydroxykynurenine (3-HK) and 3-HANA can increase lipid peroxidation and AA resulting in increased production of prostaglandins [162].

Kynurenine pathway and insulin resistance

The KYN pathway has been implicated in a range of diseases and disorders including: acquired immune deficiency syndrome (i.e. AIDS), dementia, Alzheimer's disease, Huntington's disease, schizophrenia, depression, anxiety, multiple sclerosis, rheumatoid arthritis, cardiovascular disease, amyotrophic lateral sclerosis, neoplasia and hypotension [41,121]. However, of interest here is the additional finding that KYN metabolites have also been linked to both metabolic syndrome [162], and migraine [65,51,52].

In the last few years is has become evident there may be a relationship between metabolic syndrome and migraine [82]. Metabolic syndrome patients may be at increased risk of cardiovascular disease [149], stroke [83], hypertension [5] and migraine [82]. Several definitions of the metabolic syndrome have been proposed, which has caused some confusion. However, the pathophysiology for metabolic syndrome almost always includes impaired insulin sensitivity or insulin resistance [5].

Insulin resistance is a known risk factor for hypertension [132], stroke [108], cardiovascular disease [73], metabolic syndrome [82] and migraine [179]. Thus, insulin resistance could hold the key to understanding the co-morbidity between migraine and these other conditions [191].

Dysregulation of the Trp-KYN pathway and KYN-NAD pathway is associated with insulin resistance [154]. A significant positive relationship has been reported between KYN and insulin resistance with a higher KYN level shown to be associated with higher body mass index and HOMA2-IR insulin resistance index scores [64].

Pyridoxal-5-phosphate (P5P), an active form of vitamin B6 is needed as a co-factor to activate the key enzymes of KYN-NAD pathway. Moreover, an absence of P5P redirects KYN-NAD metabolism to production of XA, a metabolite known to impair synthesis, release and activity of insulin [163].

When KYN metabolites were compared in chronic migraineurs (N = 119) and age-matched healthy controls (N = 84) a significant reduction in KYN, KYNA, 3-HANA, 3-HK, 5-hydroxyindolacetic acid (5-HIAA) and QUINA was noted in chronic migraineurs. Alternatively, the level of Trp, ANA and XA was significantly increased [51,52]. Thus, given that in migraineurs the level of KYNA and 3-HANA is significantly reduced and XA is significantly increased [51,52], the data confirms that the level of NO [158] and risk of insulin resistance [163] in migraineurs may be increased.

Section 3: Migraine triggers and glucoregulation

Fukui et al. [70] assessed 200 migraineurs (162 women, 85 men) and found that the most common group of migraine triggers (reported by both genders), could be classed as nutritional triggers. The

nutritional triggers in order of frequency were fasting, chocolate, alcohol/red wine and coffee. Other factors such as stress, citrus, cheese, monosodium glutamate, aspartame, menstrual cycle (females), nuts and nitrates were also thought to be able to promote a migraine attack. Space does not permit an investigation of all migraine triggers. Therefore, in the next few sections a selection of the most common migraine triggers identified by Fukui et al. [70] will be investigated in the context of glucoregulation.

Fasting and skipping meals

An overnight fast can act as a migraine trigger in vulnerable individuals [176]. Indeed, it has been known for some time that fasting and the missing of one or more meals can promote the development of migraine [49,27,28,141]. A migraine attack often occurs after an overnight fast and the majority of migraine attacks have been noted between 0600 h and 1200 h [207]. Consistent with these claims later studies found that more than 48% of migraine attacks reportedly occur between 0400 h and 0900 h [68].

An increase in histamine is commonly observed in migraine. Similarly, the level of histamine is often elevated during a migraine attack [158]. Plasma histamine levels reportedly increase in the early hours of the morning (Rehn et al., 1987). One of the roles of histamine is to promote glucose transport and an elevation in histamine can occur in order to assist cells when presented with a metabolic challenge [221].

Reactive hypoglycemia

Hypoglycemia was claimed to be a common precipitating factor in migraine headaches as early as 75 years ago [48]. Later studies confirmed that a large percentage of migraineurs showed signs of being hypoglycemic (Include reference 173 (i.e. Pearce, 1971) so the line reads: Later studies confirmed that a large percentage of migraineurs showed signs of being hypoglycemic (173), due to hyperinsulinism (185).) due to hyperinsulinism [185]. However, it was not until a decade later that new evidence emerged suggesting migraine can be triggered by a sucrose-induced reactive hypoglycemia [57].

Reactive hypoglycemia is a relatively uncommon meal-induced hypoglycemiac disorder. Patients are characterized as ingesting excessive quantities of refined carbohydrate and hyperinsulinism usually accounts for the hypoglycemia. The recommended treatment usually involves dietary restriction of refined carbohydrates. However some patients may require medication [92].

Hyperinsulinemia, diabetes mellitus and hyperlipidemia are known to incite vertigo, tinnitus, and hearing loss [107]. An investigation into the cause of vestibular dysfunction found that 90% of patients had either an abnormal glucose tolerance test or an abnormal insulin level [178].

A relationship between hyperinsulinemia and migraine with tinnitus and/or vertigo has previously been suggested [119]. Migraine sufferers often report the presence of vestibular symptoms such as vertigo [71,220]. However, the vertigo does not appear to be related to the visual disturbance associated with aura [155].

Less specific symptoms of dizziness and head motion intolerance have also been reported in migraineurs [46]. However, in these instances it was claimed the dizziness could be related to hypotension, anxiety disorders or major depression, all of which have an increased prevalence in migraine patients [155].

Refined sugar products

Clinical evidence suggests that the consumption of sucrose can promote a significant elevation in serum insulin in fasted female migraine sufferers. However, while the level of serum insulin in female migraineurs was noted to be significantly higher than males and controls there was no evidence of sucrose-induced hyperinsulinism in any of the participants [114,113].

The size of the carbohydrate molecule can influence the postprandial glucose and insulin response such that more complex carbohydrates elicit lower responses [148]. The consumption of sucrose can produce higher blood sugar readings than other carbohydrates such as fructose or honey due to sucrose-induced glucose intolerance [201] and insulin resistance [193].

Comparisons with starch show that the consumption of sucrose can result in a 20% increase in the insulin level [44]. FFA synthesis is also increased [98], which could significantly increase histamine production [239], inhibit glucose utilization and oxidation in muscle, and promote gluconeogenesis in liver [140]. Sucrose feeding enhances lipogenesis in the liver and promotes an increase of the lipid concentration in liver and blood [228]. Lipogenic enzyme activity is significantly higher with sucrose [184,161]. Moreover, the level of fasting triglycerides (cholesterol), VLDL, LDL and HDL of males (not females) is positively correlated with the amount of sucrose in the diet [182].

Sucrose-fed animals exhibit significantly higher fasting serum insulin, plasma glucose and plasma triglyceride levels and significantly lower insulin sensitivity [85]. Additionally, sucrose-fed animals demonstrate greater body weight and higher levels of non-fasting insulin and glucose and 6-h fasted triglyceride [183].

However, when sucrose is combined with fat the level of insulin is potentiated and relatively low amounts of sucrose and fat can produce a significantly higher insulin response when compared to sucrose alone [84]. Therefore, while sucrose alone may not promote hyperinsulinism in migraineurs [113], food products such as chocolate, which contain a large amount of sucrose and fat [35], could potentiatie the level of plasma insulin further and promote the

development of reactive hypoglycemia due to hyperinsulinism-induced insulin resistance. Furthermore, if we consider that chocolate also contains histamine [169], the relationship between chocolate-induced reactive-hypoglycemia and migraine becomes even more plausible.

Sucrose-induced insulin resistance

The link between refined sugar and metabolic syndrome is well established [139]. Sucrose consumption can promote insulin resistance in humans [197] and animals [39]. Therefore, reducing the amount of refined sugar in the diet often forms part of the metabolic syndrome patient's treatment [139]. Similarly, sucrose is a known migraine trigger [185] and eliminating sucrose from the diet can result in a significant decrease in migraine symptoms [57] and need for pain medication [112].

Migraine sufferers often report cravings for food high in refined sugar and then a migraine develops later [105]. It has recently been reported that a population of glutamatergic neurons that contain GLUT2 and project to the nucleus accumbens have been identified in the rodent paraventricular thalamus. Of interest here is the finding that these neurons are activated by hypoglycemia and their inactivation by *Slc2a2* increases motivated sucrose-seeking but not saccharin-seeking behaviour [122].

Clinical data suggests that the consumption of sucrose by male and female migraineurs can result in a significant and immediate decrease in the glucose/insulin (G/I) ratio and increase in insulin/cortisol (I/C) ratio in all participants [113] with lower G/I ratio [14,142] and higher I/C ratio [75] depicting higher degrees of insulin resistance. However, gender differences in insulin sensitivity can emerge over time with the G/I ratio at 135-min and 150-min noted to be significantly lower and I/C ratio in general significantly higher in female migraineurs [113]. Thus, the effect of sucrose on insulin sensitivity in male and female migraineurs is not the same and significant differences in insulin sensitivity emerge in female migraineurs at approximately 120-min post-sucrose consumption.

Red and white wine

Alcohol is a commonly reported migraine trigger ((Fukui et al., 2010) should read (Fukui et al., 2008) - in the reference list currently as 70)(Fukui et al., 2010) and red wine (in particular), can provoke a migraine attack in more than 80% of the 11 migraineurs assessed [134]. The biochemical data confirms that both red wine and white wine can alter glucoregulation. However, the effect of red wine and white wine on energy metabolism and utilization is not the same. Indeed there is increasing evidence to suggest that the effect of wine on glucoregulation is influenced by not only the nutritional content of the alcoholic beverage but also the nutritional status of the individual at the time of wine ingestion [111,117], two factors that are rarely considered in alcohol research.

Most alcoholic beverages contain some histamine. However, red wine is unique because it not only contains the highest amount of histamine [230] it is also one of the few alcoholic beverages that can promote histamine release [99]. An elevation in histamine usually occurs when cells are presented with a metabolic challenge [221]. Thus, the data could be highlighting that consuming red wine may alter energy metabolism and utilization in some way.

The elevation in histamine that has been noted when red wine is consumed is not surprising when we consider that red wine contains resveratrol, a potent anti-oxidant with known hypoglycaemic and hypolipidemic properties [214]. The administration of resveratrol in diabetic animals can promote a simultaneous decrease and increase in plasma glucose and plasma insulin, respectively [164].

The consumption of red wine under fasting conditions can significantly reduce the level of preprandial plasma glucose and serum insulin [116]. However, while both red and white wine can significantly reduce the level of postprandial plasma glucose a similar alcohol-induced lowering of postprandial serum insulin was only noted with white wine [115,117]. Moreover, when insulin sensitivity in the red wine and white wine trials was compared the level of insulin sensitivity in the white wine trial was found to be significantly higher (Reference should be: Kokavec, Halloran and Crowe, 2009)(Kokavec, unpublished data), which is at odds with the diabetic findings [33,77,151].

The effect of consuming red wine and white wine alone after a meal on the glucose-insulin relationship is not the same [116,117]. The evidence suggests that ingesting red wine can significantly alter the postprandial glucose-insulin relationship and promote the development of a pseudo-hypoglycemic condition. Alternatively, white wine promotes a pseudo-diabetic condition as evidenced by a significant lowering of insulin, which mostly likely occurs due to a wine-induced increase in insulin sensitivity.

By way of explanation I would like to offer that it is well accepted that a positive correlation exists between central 5-HT activity and peripheral insulin sensitivity [94]. Red wine can increase the level of whole blood 5-HT in migraineurs and controls [171,172]. However, the binding of 5-HT to 5-HT1 receptors is inhibited, possibly due to the presence of resveratrol [175], which could increase the risk of insulin resistance [76].

Banana

Migraine sufferers often report that eating a banana can trigger a migraine attack [112,113]. However, most of the studies have not asked patients to describe how ripe the banana is when it was consumed and have assumed the banana was ripe (i.e. yellow in color). The ripeness of bananas is important because as we will see in the next few paragraphs there is a difference in nutritional content between green bananas and yellow bananas, which has the

potential to impact insulin sensitivity.

The banana fruit starts off as being green and then slowly changes to yellow as the fruit ripens. The developing fruit contains a high concentration of tannins [200], which is known to significantly reduce 5-HT activity [186] and as a consequence reduce insulin sensitivity [94].

As the banana fruit develops it imports sucrose to produce starch. Then when the banana fruit is fully formed it go through a process called ‘climacteric’. The process includes the starch in bananas being broken down and sucrose accumulating in the tissue. There is a burst of respiration, which fuels the ripening process. Therefore, the major carbohydrate in ripe bananas is sucrose [200], the consumption of which is known to promote insulin resistance (e.g. [193].

Peanuts

Decreased dietary fat is associated with statistically significant decreases in headache frequency, intensity, duration, and medication intake [24]. Therefore, given that the nutritional content of peanuts includes about 47% fat, 25% protein, 19% carbohydrate and 7% water [11], it is not surprising that peanuts can instantly provoke a migraine attack in vulnerable individuals [114,113].

Oleic and linoleic acids are the most abundant fatty acids in peanuts [11] while the carbohydrates in peanuts include starch, pectin, cellulose and sucrose [153]. Early studies detected the presence of sucrose, fructose and glucose in peanuts. Later studies confirmed that sucrose was the major soluble sugar constituent in peanuts followed by glucosamine, stachyose, and raffinose. The insoluble fraction contained glucosamide, arabinose and trace levels of glucose and rhaminose [153].

As noted above, peanuts contain glucosamine, a product of glucose metabolism via the hexosamine pathway that is known to impair insulin-induced GLUT4 transport translocation to the plasma membrane and induce insulin resistance [17,6]. Furthermore, peanuts contain a combination of fat and sucrose [11,153], which is known to promote hyperinsulinism [84], and increase the risk of insulin resistance [193].

Aspartame and monosodium glutamate

Aspartame found in food can instantly provoke a migraine attack [199]. Similarly, food containing monosodium glutamate (MSG) is also a commonly reported migraine trigger that can promote the development of migraine symptoms almost immediately [199].

Ingesting aspartame can increase the supply of phenylalanine, which subsequently can promote a decrease in tryptophan uptake by brain tissue or a depression in tryptophan conversion to 5-HT [202]. Aspartame has been shown to significantly impair the release of 5-HT in several brain regions [21] and reduce NPY activity in the ARC [19]. Thus, aspartame can promote a decrease in glucose sensing in the ARC [150] and by reducing activity at 5-HT receptors could encourage the development of insulin resistance [76].

Rodent studies have shown that MSG can reduce the activity of lactate dehydrogenase in liver and serum and increase the activity of glucose-6-phosphate dehydrogenase, which results in increased biosynthesis of fatty acids and subsequent shift in carbohydrate metabolism towards lipogenesis (Reference (Malik and Ahluwalia, 1994) should be 138 (i.e. Malid and Ahluwalia, 1994))(Malik and Ahluwalia, 1994). Furthermore, a combination of MSG and a hypercaloric diet can induce an alteration in the metabolic rate of glucose utilization [59]. MSG-treated mice show a significantly reduced GLUT4 content in the absence of any change in the amount of GLUT-1, which suggests that MSG may promote insulin resistance [137]. MSG can cause a brief but significant dose-dependent decrease in glucose uptake by the brain. Similar to aspartame, damage from MSG is prominent in the ARC, pre-optic nucleus, and the median eminence [45].

Caffeine

Drinking coffee prior to having an OGTT can significantly increase circulating levels of epinephrine and stimulate lipolysis. Caffeine ingestion was also shown to significantly exaggerate the plasma insulin response during the OGTT. However, the significant elevation in plasma insulin during the OGTT was not associated with any corresponding lower in blood glucose with plasma glucose remaining unchanged or even becoming slightly elevated in some participants [81].

Caffeine ingestion can increase brain levels of tryptophan, 5-HT, and 5-hydroxyindoleacetic acid in a dose-dependent fashion [195]. The ingestion of caffeine can decrease cerebral blood flow and promote an increase in brain glucose use [56]. Under these conditions insulin resistance can occur due to the caffeine-induced increase in circulating levels of epinephrine [23].

Cheese

Cheese contains histamine and the presence of histamine-producing bacteria in cheese is a key factor in histamine production. Lactobacilli play a significant role in histamine formation in Gouda cheese. Moreover, cheese

ripening temperature, pH, and salt concentration may influence the ability of lactobacillus to produce histamine. Lastly, cheese storage temperature plays a role in histamine production with higher temperatures found to increase histamine content [216].

Citrus

Citrus is a common migraine trigger [145,134]. Most citrus fruits are high in vitamin C and potassium and are a good source of folate, iron, calcium and other minerals. However, nutrients such as vitamin C can elevate NO levels [229], which could promote a significant decrease in glucose transport and metabolism [125], and promote insulin resistance.

Of the citrus fruits grapefruit is the most studied in the general population because it is thought to contain a number of protective plant chemicals. Grapefruit is high in fibre, low in calories and contains phenolic acid, limonoids, terpenes, monoterpenes and bioflavonoids [86]. The major bioflavonoid found in grapefruit is naringen (4′,5,7-trihydroxyflavanone), which gives the fruit its bitter taste. Naringen can promote antioxidant activity, lower blood lipids and decrease the plasma glucose level. Thus, Naringen has potent hypoglycemic and hypolipidemic properties [86].

Naringen is known to inhibit insulin-stimulated glucose uptake in 3T3-L1 adipocytes in a dose-dependent manner by inhibiting the activity of phosphoinositide 3-kinase (PI3K), a key regulator of insulin-induced GLUT4 translocation. Thus, regular consumption of grapefruit could potentially promote insulin resistance in susceptible individuals via impaired glucose uptake in adipose tissue [88].

Naringen has also been shown to inhibit the action of Cytochrome P450 (CYP450), which may result in severe drug interactions in vitro due to inability to breakdown some medications. CYP450 enzymes are present in most body tissues and play an important role in hormone synthesis and breakdown (including estrogen and testosterone synthesis and metabolism).

The metabolism of estrogen mainly occurs in the liver, where the majority of CYP450 is expressed. The regulation of CYP450 enzymes is by estrogen at the estrogen receptor, which suggests that CYP450 may be related to homeostasis of estrogen at local organs. Thus, any alteration in CYP450 could significantly influence estrogen synthesis and metabolism [223], which in turn could alter feeding behaviour [62] and insulin sensitivity [72].

Following hypoglycemia the production of prostaglandin, a substance that causes inflammation, is decreased [232]. Ironically, grapefruit fruit peel can significantly block prostaglandin production [86], due to the presence of nobiletin, a ~~flavanoid~~ flavonoid found in the peel of most citrus fruit [100].

Magnesium deficiency

During hypoglycemia, Mg2+ [26] and the concentration of phosphocreatine and ATP is reduced [177]. Similarly, a chronically decreased phosphocreatine:ATP ratio has been observed in migraineurs [225] and Type I diabetics [26]. The level of Mg2+ in erythrocytes prior to a migraine attack is significantly lower in migraine without aura patients when compared to other headache sufferers [196]. However, during a migraine attack there is more consistency with a reduction in Mg2+ noted in both migraine with and without aura patients [180].

Low magnesium (Mg2+) has been linked to a number of chronic diseases, including migraine, stroke, hypertension, cardiovascular disease, type 2 diabetes mellitus and metabolic syndrome [16]. Mg2+ plays a critical role in maintaining nerve and muscle function, cardiac excitability, neuromuscular conduction, muscular contraction, vasomotor tone, blood pressure, bone integrity, and glucose and insulin metabolism [165].

The link between magnesium deficiency and type 2 diabetes is well established [227]. Mg2+ plays a significant role in glucose and insulin metabolism by impacting tyrosine kinase and phosphorylase b kinase activity. Additionally, Mg2+ can significantly alter expression of GLUT4, with Mg2+ helping to regulate glucose translocation into the cell [36]. A significant reduction in Mg2+ can impair glucose utilization and insulin sensitivity [210]. Thus, the magnesium data suggests that glucose utilization and insulin sensitivity may be significantly altered in migraineurs.

Menstrual cycle

Regular hormonal fluctuations associated with the menstrual cycle can influence appetite and food intake [62]. Changes in 5-HT concentration has been reported during the menstrual cycle with the level of 5-HT lowest in the post-ovulatory or premenstrual phase of the cycle [217]. Energy expenditure and food intake is also higher in the post-ovulatory phase when compared to the pre-ovulatory or follicular phase [231].

Estrogen, a female sex hormone synthesized by the hypothalamic-pituitary-gonadal axis, similar to 5-HT has been shown to decrease carbohydrate intake [30] and promote insulin synthesis and release [8]. However, estrogen treatment can significantly decrease the level of NPY in the PVN. Thus, modulation of food-intake by estrogen could be mediated by altered NPY release locally from nerve terminals in the PVN [30].

Abrupt falls in estrogen can trigger a migraine attack [166]. Additionally, women commonly report developing migraine symptoms during the second half of their menstrual cycle in the premenstrual or luteal phase [47], when estrogen is low [74]. A significant alteration in insulin sensitivity has been noted during the menstrual cycle. The release of estrogen can improve insulin sensitivity [72], with decreased receptor binding observed in the luteal phase [62], when the risk of developing migraine is increased [47].

The taking of oral contraceptives is also a known migraine trigger [20] and in particular can be potentially hazardous for migraine with aura patients [7]. Cyclic fluctuations in sex hormones are absent or minimized in oral contraceptive users. Furthermore, significant cycle-related trends are not observed in women using oral contraceptives [10].

When the concentration of estrogen and progesterone is raised either artificially as in oral contraceptive use or naturally as in pregnancy, insulin sensitivity is impaired [62]. Thus, women are more likely to develop migraine symptoms when the risk of developing insulin resistance is also increased.

Emotional stress

Emotional stress can trigger a migraine in vulnerable individuals [145,112]. Cortisol, a glucocorticoid known to play a role in energy metabolism and utilization [53], is rapidly released in response to emotional stress [226]. Hypercortisolism is a common finding in migraine patients [242]. However, an increase in cortisol can promote activity away from 5-HT synthesis and activate the Trp-KYN pathway.

The function of insulin in the brain may be to assist in glucose homeostasis by regulating cerebral glucose metabolism and regulating feeding. Insulin can lower food intake and body weight and an absence of circulating glucocorticoids can increase the brain's sensitivity to insulin [40]. Alternatively, cortisol excess can inhibit glucose utilization and transport [95,226], which in turn can promote insulin insensitivity, induce hypoglycemia due to increased demand for glucose, and result in decreased excitability of brain cells [93].

Summary

The aim of this paper was to attempt to stimulate discussion on the relationship between migraine and energy metabolism and utilization by proposing that migraine may be part of a cascade of events, which together act to protect the organism when confronted by a metabolic challenge. From the evidence presented above it would appear that most of the common migraine triggers can be linked to less than optimum energy metabolism and utilization in some way.

More than 95% of migraineurs can identify at least two migraine triggers [70] suggesting there may be a metabolic relationship between migraine triggers [38]. Earlier Peatfield [174] highlighted the possibility that migraine triggers can be grouped and even suggested there could be a relationship between red wine, cheese and chocolate. Indeed, as this review has revealed both of these claims could be true in that there does appear to be a metabolic relationship with red wine [230], cheese [216] and chocolate [169], all known to contain histamine.

This review has been successful in showing that the biochemical changes that occur before and during a migraine attack are consistent with the development of a metabolic challenge. Most (if not all) of the migraine triggers could potentially reduce insulin sensitivity (e.g. sucrose, red wine, peanuts, menstrual cycle, oral contraceptives, bananas, aspartame, glucosamine, monosodium glutamate, caffeine, citrus, emotional stress), which could ultimately influence GLUT4 activity in vulnerable individuals.

It is very tempting to conclude that activation of the Trp-KYN pathway and insulin resistance is one of the underlying factors in migraine. Metabolism of Trp via the Trp-KYN pathway is promoted when cortisol is elevated and hypercortisolism has been noted in migraineurs [242]. In migraineurs the level of KYNA and 3-HANA is significantly reduced and XA is significantly increased [51,52], which further suggests that the level of NO [158] and risk of insulin resistance [163] in migraineurs may be increased.

However, how the migraine triggers promote insulin resistance does not appear to be the same in all cases. Moreover, sex differences with respect to the ability of sucrose, a substance known to promote insulin resistance in humans [197] and animals [39], to promote insulin resistance in migraineurs have been reported (e.g. [113]. Thus, migraine may be a highly unique and complex disorder.

The material presented in this review is by no means extensive and has merely focussed on some of the more established biochemical aspects of energy metabolism and utilization. There are many biochemical factors that could have been examined in this review (e.g. leptin, ghrelin, cholecystokinin) and probably many more factors that remain to be discovered. However, the information that has been presented serves as a good starting point to perhaps make us start to review the current treatment and management of migraine patients.

Uncited references

[118,138,173,206].

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Highlights

- Migraine is associated with the development of a metabolic challenge.
- Migraine triggers can differentially alter energy metabolism and utilization.
- Common factor linking triggers is an ability to promote insulin resistance.
- Insulin resistance may underlie the pathogenesis of migraine.

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